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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,355	01/26/2001	David A. Zarling	A-68872-1/RFT/RMS/BTC	6076

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FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP
Four Embarcarero Center, Suite 3400
San Francisco, CA 94111-4187

EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,355	ZARLING ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on th cover she t with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 10-15 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-9 and 16-18 have been cancelled by applicant in the response filed April 8, 2003 as Paper No.10. Claims 10-15 are pending and under consideration in the instant application.

Priority

Applicant's claim for domestic priority to provisional application US 60/178,561 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statement filed February 24, 2003 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Objections

Claim 15 is objected to because of the following informalities: the term "hologenated" appears to be a misspelling of halogenated. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The instant invention is drawn to a method of inhibiting cancer by administering an inhibitor of Rad51. The invention requires that individuals suffering from all types of cancers can be effectively treated by administering a simple compound, effectively indicating the discovery of a "magic bullet" for all kinds of cancer.

Scope of the invention. The scope of the invention is incredibly broad, suggesting that the ability to cure any cancer is linked directly or indirectly to the inhibition of Rad51. However, cancers have distinct etiologies and many even have unknown etiologies.

State of the art. A review of the prior art reveals many complications involving the treatment or inhibition of cancer as an inclusive disease. Pervaiz (*Curr. Pharm. Des.* **8**: 1723-1734, 2002; henceforth Pervaiz) teaches that the initiation, promotion and progression of cancer is an intricate process involving a dynamic process of changes in the host genome and responses (or lack thereof) to cellular growth signals (see for example page 1723, the first paragraph of Pervaiz). Pervaiz additionally points out that cancer is not a single disease, and that there are a complexity of pathways involved in the etiology of different cancers in different tissues, and that methods for treating such a diverse population of diseases (under the moniker of cancer) reflects a need for a diverse form of treating or curing the diseases (again see page 1723, the first paragraph of Pervaiz). Pervaiz also teaches that although the chemotherapeutic agents currently used in treatments of various cancers are developed with the differences in types of cancers in mind, the existing compounds still do not exhibit a desirable level of selectivity for the cancer cells (see for example page 1724, first full paragraph of Pervaiz), suggesting that normal cells are also at risk to the toxicity of these anti-cancer agents. The skilled artisan would conclude from the teachings of Pervaiz that the specificity of cancer treatments is an important factor in the treatment or inhibition of any given cancer, let alone the conglomeration of all diseases characterized as cancers. Additionally, the prior art raises a number of other issues regarding the effectiveness of cancer treatments which are not addressed in the instant specification. For instance, multi-drug resistance and the inactivation of anti-cancer agents remain a constant problem in the treatment of cancer. For instance, cisplatin and carboplatin, two drugs that are frequently used chemotherapeutically, often lose their effectiveness over time as a result of pharmacological inactivation and decreases drug accumulation (see for example Perez, *Eur. J. Cancer* **10**: 1535-

1542, 1998; see especially the Abstract; henceforth Perez). Furthermore, both cisplatin and carboplatin have minimal activity against certain types of cancers (see for example page 1535, first paragraph of Perez). Sarkadi *et al.* (*Cancer Biol.* **8**: 171-182, 1997; see entire document; henceforth Sarkadi) teaches that multidrug resistance arising from the enhanced activity of the MDR and MRP proteins often plagues the effectiveness of chemotherapy, often leading to drug resistant tumors (see for example page 171, the first and second paragraphs of Sarkadi). There are no teachings in the instant specification to address these issues, or other issues involving the treatment and inhibition of cancer, as it regards the use of small molecule inhibitors of Rad51. As a result, the skilled artisan would conclude that the prior art does not enable the instant specification as it regards the claimed method.

Number of working examples and Guidance provided by applicant. There are no working examples provided in the instant specification, and there is no guidance as to the predictability of the invention. The instant specification prophetically surmises that the application of a small molecule inhibitor of Rad51 will result in the treatment or inhibition of all cancers, without even the most rudimentary of data. There is no discrete discussion of what the role of Rad51 is during the progression of cancer in the instant specification. The specification briefly discusses the role of Rad51 in the process of recombinational repair, that it is an essential protein, and that it associates with proteins that have been implicated in tumorigenesis. Specifically, the specification suggests that the p53 protein, through its interaction with Rad51, downregulates recombinational repair along the pathway to apoptosis (a.k.a., programmed cell death); however, there is no nexus between this prediction and the ability to treat cancer by inhibiting or treating cancer, and there is no scientific evidence for this prediction aside from the physical interaction

of p53 and Rad51. This is further complicated by the fact that there are hundreds of type of cancers that have distinct etiologies, many of which are unknown and most of which will be independent of the biological activities of Rad51. Therefore, the instant specification provides no guidance of examples that the inhibition of Rad51 will have any effect towards the treatment or inhibition of any types of cancer.

Furthermore, Rad51 is an important protein for recombinational DNA repair in normal eukaryotic cells. The instant specification provides no guidance on how to properly administer a small molecule inhibitor of Rad51 so that the inhibitor will specifically target tumor cells selectively, and therefore not negatively affect normal cells. There is no contemplation in the specification regarding how to prevent the inhibition of Rad51 in normal cells, wherein the repair activities of Rad51 may be important for repairing a mutation in an oncogene in the cell. Without such teachings, it is unpredictable that the molecule will treat or inhibit a cancer cell without killing non-tumor cells, or without transforming non-tumor cells into cancerous cells due to the inability to properly repair a mutation in an oncogene. There is no demonstration of efficacy *in vivo* in a human, or even an art-accepted animal model, and no demonstration of efficacy *in vitro* for any small molecule inhibitors of Rad51. As a result, the skilled artisan would not be able to treat or inhibit cancer by administering a small molecule inhibitor of Rad51 to cells based solely upon the teachings of the instant specification, because there is no indication that these molecules have any efficacy in the treatment or inhibition of cancer whatsoever.

Level of skill in the art. The level of skill in the art is highly underdeveloped. This is true for the treatment of cancer as whole, which is evidenced by the fact that cancer is the second leading cause of death (behind cardiovascular disease) in the United States of America. If the level of

skill in the treatment or inhibition of cancer was high, or was as simple as administering a small molecule inhibitor of Rad51 such as a nucleoside diphosphate, cancer would not be such a prevalent cause of death.

Unpredictability of the art and Amount of experimentation required. There is a tremendous amount of experimentation involved, all of which is undue and unpredictable trial and error experimentation. The skilled artisan would be required to test the efficacy of all small molecule inhibitors of Rad51 randomly, with the hope that even one would effectively treat or inhibit all or any types of cancer. There is no indication in either the prior art or the instant specification that a small inhibitor of Rad51 will have any effect towards the treatment or inhibition of cancer. Rather, the prior art is replete with teachings on how difficult a problem the treatment and inhibition of cancer is, and how diverse the treatments are for different types of cancer. The instant specification does not effectively address how to circumvent any of the typical problems associated with the treatment or inhibition of cancer, as outlined above, as it regards the use of small molecule inhibitors of Rad51. In the absence of any direction by the instant specification, the claimed invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claims 10-15 are dependent on a cancelled claim. Therefore the metes and bounds of the claim are indefinite, as it is unclear what exactly the method encompasses. In the interest of compact prosecution, the examiner presumes that the limitations that are set forth in the preamble of former claim 1 will be incorporated into pending claim 10 (and its depending claims). Specifically, the examiner will interpret the claims as being drawn to a method for inhibiting or reducing tumor cell proliferation in an individual in vivo comprising: administering a Rad51 inhibitor that is a small molecule, and a polynucleotide capable of expressing functional p53 protein.

Claims 10-15 are indefinite because they do not contain a step that positively refers back to the preamble of the claim. For instance, the method is drawn to the treatment or inhibition of cancer in vivo, yet there is no step in the method whereby cancer is treated of inhibited in vivo. As such, the metes and bounds of the claim are indefinite because it is unclear what the ultimate step of the method is.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
June 27, 2003

PATENT EXAMINER
Gerald G. Letters
A.U. 1636